

REMARKS

Claims 23, 24, 26 and 28-37 have been examined. Applicants request reconsideration of the claims in view of the remarks below. This communication is being filed in response to the non-final Office action dated September 1, 2010.

Rejections Under 35 U.S.C. § 103:

Claims 23, 31, 32, and 33 - 37 remain rejected under 35 U.S.C. § 103(a) as being obvious over Sallusto *et al.* in view of Bigotti *et al.*, as evidenced by Inaba *et al.*, for reasons already of record. The Examiner has considered the prior arguments provided by Applicants and considers them non-persuasive. In particular, the Examiner has objected to the lack of "objective evidence" showing that Langerhans cells stained with anti-S-100 antibody, some of them directly in contact with prostate tumor glands, and most adjacent to the prostate tumor glands, as taught by Bigotti *et al.* are immature antigen presenting cells. In addition, the Examiner has noted that in the presence of antigen, immature antigen presenting cells are capable of pick up and processing the antigen citing Sallusto *et al.* Further, the Examiner has asserted that it is well known in the art that necrotic cancer cells shed cancer antigens into their vicinity and circulation and that Applicants do not have objective evidence that Langerhans cells at the vicinity of prostate cancer glands did not pick up the antigen during their journey from the skin or epidermis to the vicinity of prostate cancer glands.

Still further, the Examiner alleges that although Bigotti *et al.* do not directly teach that Langerhans cells, in the vicinity of prostate cancer cells capture prostate cancer antigen, and present prostate cancer antigen to T cells, Bigotti *et al.* teaches: i) the presence of Langerhans cells and HLA class II molecules correlates with low grade prostate cancers, as compared with high grade prostate cancers, and ii) such correlation is understandable in view of (a) Langerhans cells and HLA class II molecules elicit the immune response, capable of direct antigen

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presentation to immune cells, (b) Langerhans cells act as antigen presenting cells in neoplastic environment, and (c) HLA class II molecules expressed by neoplastic glandular epithelium, with the aid of Langerhans cells, interact with macrophages and with T helper lymphocytes, and cause expansion of cytotoxic T cells and enhancement of antibody response to membrane-bound tumor associated antigen.

The Examiner proceeds to allege that such suggestion by Bigotti *et al.* that Langerhans cells, being antigen presenting cells and eliciting the immune response, could contribute to controlling cancer growth in prostate cancer clearly provides motivation for making dendritic cells specific for prostate cancer antigen *in vitro*, using the method of making dendritic cells taught by Sallusto *et al.* with prostate antigen, for use in inducing an anti-tumor immune response for treating cancer.

In regard to Applicants argument that many tumors, including prostate tumors, secrete IL-10 and other cytokines that down regulate the immune response against tumor, as taught by Sharma *et al.* and Steinbrink *et al.* (both previously submitted). The Examiner asserts that the effect of IL-10 on T cell response in cancers, whether suppression or stimulating the immune response, depends on the types of tumor (citing Steinbrink *et al.*, page 1640, third and fourth paragraph).

Concerning the argument that Bigotti *et al.* did not detect infiltrating lymphocytes which might indicate that antigen presenting cells might have successfully taken up and processed prostate antigen for presentation to naïve T cells, the Examiner has asserted that Applicants have not provided objective evidence or references showing that activated CD4+ T cells and CD8+ T cells and activated B cells producing antibodies have to be present right at the site of the prostate glands. In addition, the Examiner has alleged that one would have expected that the dendritic cells prepared *In vitro* as taught by the combined art would successfully present the prostate

cancer antigen and activate T cells, in view of the teaching of Sallusto *et al.* that culture dendritic cells are most efficient for presentation of antigens, and cause proliferation of T cells, and further in view that it is the properties of dendritic cells to activate CD4+ T cells and CD8+ T cells, as taught by Inaba *et al.*

Still further, in regard to the argument that it was well known that Langerhans cells were present in normal prostate, the Examiner has asserted that Applicants have not provided any objective evidence that Langerhans cells are activated and present normal prostate antigen in normal prostate environment. In addition, the Examiner alleges that Bigotti *et al.* teach that Langerhans cells act as antigen presenting cells in a neoplastic environment.

In addition, the Examiner has alleged that Applicants have misrepresented the Examiner's reasons for rejecting the claims based on Troy(er) *et al.* In particular, the Examiner has objected to Applicants interpretation of her prior remarks regarding Troy(er) *et al.* The Examiner asserts she did not state that Langerhans cells stained with the anti-S-100 antibody, some of them are directly in contact with prostate tumor glands, and most are adjacent to the prostate tumor glands as taught by Bigotti *et al.* are immature antigen presenting cells. Instead, the Examiner as above, alleges that Applicants response does not have any objective evidence showing that Langerhans cells stained with the S-100 monoclonal antibody are immature dendritic cells. Further, the Examiner alleges that the prostate cancers taught by Troy *et al.* are high grade prostate cancers, having Gleasons scores of 4 - 8. The Examiner notes that Bigotti *et al.* did not find Langerhans cells in high grade prostate cancer, such as grades 4 and 5.

Applicants must again strongly disagree with the Examiner's summary and conclusions regarding the teachings of Bigotti *et al.* First, Applicants do not believe that there is any requirement that "objective evidence" be presented demonstrating that the Langerhans cells (S-100-staining cells) present in low grade prostate tumor tissue by Bigotti *et al.* To the contrary it

is a requirement that the Examiner present a *prima facie* case of obviousness before Applicants must present objective evidence to overcome the objection. In the present rejection, the Examiner has noted that in the presence of antigen, immature antigen presenting cells are capable of pick up and processing the antigen citing Sallusto *et al.* and further that it is well known in the art that necrotic cancer cells shed cancer antigens into their vicinity and circulation and that Applicants do not have objective evidence that Langerhans cells at the vicinity of prostate cancer glands did not pick up the antigen during their journey from the skin or epidermis to the vicinity of prostate cancer glands. It is well known in the art that immature antigen presenting cells pick up and process antigen, but there is no teaching in Bigotti *et al.* to suggest or disclose that the S-100 binding cells are picking up or processing antigen. Further, while necrotic cells may release their cell contents into their vicinity and circulation no prostate tumors disclosed by Bigotti *et al.* as having S-100 binding cells are grade 1 and grade 2 prostate tumors that do not comprise necrotic cells. As such, any action of necrotic cells is not relevant to the present rejection. Attached hereto is a Declaration by Marnix L. Bosch which addresses this issue in paragraph 3. As such, until the Examiner has made a proper case of *prima facie* obviousness there is no requirement for Applicants to provide objective evidence to prove a negative.

In regard to Bigotti *et al.* teaching: i) the presence of Langerhans cells and HLA class II molecules correlates with low grade prostate cancers, as compared with high grade prostate cancers, and ii) such correlation is understandable in view of (a) Langerhans cells and HLA class II molecules eliciting the immune response, capable of direct antigen presentation to immune cells, (b) Langerhans cells acting as antigen presenting cells in neoplastic environment, and (c) HLA class II molecules expressed by neoplastic glandular epithelium, with the aid of Langerhans cells, interact with macrophages and with T helper lymphocytes, and cause expansion of

cytotoxic T cells and enhancement of antibody response to membrane-bound tumor associated antigen. Bigotti *et al.* does no more than to demonstrate that S-100 binding cells are present in low grade prostate tumors and not in high grade prostate tumors. In paragraph 6 of the Bosch Declaration each of the above points raised by the Examiner is discussed and in paragraph 7, Dr. Bosch is of the opinion that the immune mechanism discussed by the authors is merely speculative and has no evidence for support in the article. Further, Dr. Bosch states that the skilled artisan at the time of filing the present application would have known that i) antigen presenting cells, including Langerhans cells, were present in normal glandular tissue, ii) when contacted by a foreign antigen, the antigen presenting cell would take up and process the antigen becoming activated and begin to mature, iii) the activated Langerhans cell typically would migrate to a lymphatic tissue where the cell would complete maturation, iv) upon maturation the antigen presenting cell would present antigen to T lymphocytes, including CD4+ and CD8+ T lymphocytes, wherein the T lymphocyte is activated, and v) the activated T lymphocyte, for example, a tumor infiltrating lymphocyte, migrates back to the tumor. As such, Bigotti *et al.* do no more than provide some speculation about an unsupported immune mechanism and does not support in any way or motivate to skilled artisan to combine the *in vivo* observations and speculation of Bigotti *et al.* and the *in vitro* methods described by Sallusto *et al.*

Applicants note the Examiner's comments regarding IL-10 secretion by tumors. Applicants do not acquiesce to any opinion of the Examiner about IL-10 secretion by prostate tumor cells, but as the presence or lack of IL-10 in a prostate tumor is not relevant to the present argument no additional remarks are necessary at this time.

Concerning the assertion by the Examiner that Applicants have not provided objective evidence or references showing that activated CD4+ T cells and CD8+ T cells and activated B cells producing antibodies have to be present right at the site of the prostate glands, no objective

evidence is required by Applicants until the Examiner has made a proper case for *prima facie* obviousness. In the present case the Examiner has not provided any evidence that the S-100 binding cells in Bigotti *et al.* have any function in low grade prostate tumors. As above, Bigotti *et al.* have merely speculated about an immune mechanism involving Langerhans cells, there is no evidence in Bigotti *et al.* to demonstrate to the skilled artisan that the S-100 binding cells are Langerhans cells, they do not express class II antigen, much less that the cells pick up and process prostate tumor antigen. See, Bosch Declaration, paragraphs 8 and 9.

In addition, the Examiner has alleged that one would have expected that the dendritic cells prepared *in vitro* as taught by the combined art would successfully present the prostate cancer antigen and activate T cells, in view of the teaching of Sallusto *et al.* that culture dendritic cells are most efficient for presentation of antigens, and cause proliferation of T cells, and further in view that it is the properties of dendritic cells to activate CD4+ T cells and CD8+ T cells, as taught by Inaba *et al.* As above, the skilled artisan at the time the present application was filed knew that antigen presenting cells, including Langerhans cells were present in normal glandular tissue, such as prostate tissue. It was also known to the skilled artisan that the antigen presenting cells were present in the tissue to contact and uptake foreign antigens which would activate the antigen presenting cells. Further, it was known to the skilled artisan that the activated antigen presenting cell migrated to, for example, a lymph node where contact with and activation of T lymphocytes, B cells and macrophage took place. It was also well known that it was the T lymphocytes, B cells and macrophage that were responsible for any immune response to the foreign antigen. As such, there is nothing in Bigotti *et al.*, other than their proposed immune mechanism involving macrophage, Langerhans cells and B lymphocytes that would suggest that the Langerhans cells were taking up "prostate tumor" antigens and there is insufficient evidence in Bigotti *et al.* to suggest a combination with the methods of Sallusto *et al.* to obtain the

presently claimed compositions. Evidence of the presence of CD4+ T cells, CD8+ T cells or activated B cells secreting tumor specific antibodies in any part of the body would not add evidence to make the combination of references suggested by the Examiner. (See Bosch Declaration, paragraph 11).

The Examiner has also asserted that objective evidence of Langerhans cells are activated and presents normal prostate antigen in a normal prostate environment is required. Applicants disagree that objective evidence is required as the Examiner has failed to make a *prima facie* case for obviousness. In fact, the presence of "activated Langerhans cells" in normal prostate tissue is not relevant to the present compositions or to any prior argument presented by Applicants. As discussed by Dr. Bosch in paragraph 12 of his Declaration, the question raised by Applicants is whether Langerhans cells are present in normal prostate tissues and how that number relates to the number of S-100-staining cells found by Bigotti *et al.* This is of some relevance to the rejection made by the Examiner because if there is no change between the number of Langerhans cells found in normal tissue and the number found in low grade prostate tumor than the various suggestions made by Bigotti *et al.* and the Examiner come into question. This is of particular relevance because Bigotti *et al.* make no determination as to the activation state of the S-100 cells found in the prostate tumor tissue. Further, there is no evidence in Bigotti *et al.* that the "Langerhans cells" act as antigen presenting cells in a neoplastic environment only speculation. One of skill in the art would not have found this evidence convincing of antigen uptake and processing.

Applicants has previously provided a copy of Troy *et al.* to demonstrate that active antigen presenting cells are not detected in prostate carcinoma samples and presented various arguments regarding the reference. The Examiner has noted that Applicants prior response misrepresents the Examiners reasons and that she did not state that Langerhans cells stained with

anti-S-100 antibody are immature antigen presenting cells. Applicants did not intend to misrepresent the Examiners reason for finding the prior argument non-persuasive, but regardless of whether the S-100 binding cells were activated or not, there is no teaching or suggestion in Bigotti *et al.* that any prostate antigen has been taken up or processed by these cells. As such, there is no reason for the skilled artisan to combine the *n vivo* teachings of Bigotti *et al.* with the teachings of the *in vitro* methods of Sallusto *et al.* in the manner suggested by the Examiner. See above and paragraph 13 of the Bosch Declaration. Further, Inaba *et al.* adds nothing to the teachings of Bigotti *et al.* and/or Sallusto *et al.* when considered alone or in any combination that would suggest to the skilled artisan to contact human dendritic cells with a soluble prostate antigen *in vitro* to obtain the compositions as presently claimed.

Reconsideration and withdrawal of the rejection of claims 23, 31, 32, and 33 - 37 under 35 U.S.C. § 103(a) as being obvious over Sallusto *et al.* in view of Bigotti *et al.*, as evidenced by Inaba *et al.* is respectfully requested in view of the above remarks and the attached Bosch Declaration.

The Examiner has maintained the rejection of claim 24 under 35 U.S.C § 103(a) as being obvious over Sallusto *et al.* (*supra*) in view of Bigotti *et al.* (*supra*), and as evidenced by Inaba *et al.* (*supra*), and further in view of Cohen (*Cancer Res.* 54:1055-1058, 1994). The Examiner has considered Applicants' prior response and has found it to be non-persuasive. In particular, the Examiner believes that the combination of Sallusto *et al.* and Bigotti *et al.* suggests the compositions of the claims invention as set forth above. Further, the Examiner alleges that it would have been obvious to use as prostate antigen a lysate of prostate cancer cells from a prostate cancer patient for the other reasons of record as recited above. As above, the combination of Sallusto *et al.* and Bigotti *et al.* fail to teach the compositions of the present invention. Instead, Bigotti *et al.* only speculate about the induction of an immune response in

prostate cancer and that the presence of Langerhans cells can be used to stage prostate cancer tissue. As such, any combination of Sallusto *et al.* and/or Bigotti *et al.* with Inaba *et al.* and/or Cohen *et al.* can not provide the skilled artisan with any incentive to combine the references to use a lysate of prostate cancer cells from a prostate cancer patient to make the compositions of the claim 24. Further, Cohen *et al.* teach the administration of a tumor lysate directly to a mouse. An issue at the time of filing the present application was whether antigen presenting cells contacted with a normal antigen would induce an autoimmune response to that antigen. None of the references cited by the Examiner are directed to this issue or suggest a way it might be overcome.

Claim 26 remains rejected under 35 U.S.C. §103(a) as being obvious over Sallusto *et al.* (*supra*), in view of Bigotti *et al.* (*supra*), and as evidenced by Inaba *et al.*, (*supra*), as applied to claim 23, and further in view of Lutz *et al.* for the reasons already of record. Briefly, the reasons are that the teaching of Sallusto *et al.*, Bigotti *et al.*, and Inaba *et al.* as summarized by the Examiner has been set forth above and that the Examiner has concluded that Sallusto *et al.*, Bigotti *et al.* and Inaba *et al.* suggest the compositions of the claimed invention. Therefore, the Examiner believes that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the dendritic cells taught by Sallusto *et al.*, Bigotti *et al.*, and Inaba *et al.*, using the immortalizing method taught by Lutz *et al.*, because immortalizing dendritic cells would enable maintenance of dendritic cells *in vitro* for long periods of time. As above, Sallusto *et al.*, Bigotti *et al.*, and/or Inaba *et al.* when considered either alone or in any combination do not teach or suggest the claimed presently compositions. As such, the addition of Lutz *et al.* allegedly teaching immortalization of dendritic cells can not provide the skilled artisan with the motivation or guidance to make the presently claimed composition as set forth in claim 26.

Claims 28 and 29 remain rejected under 35 U.S.C. § 103 as being obvious over Sallusto *et al.* (*supra*), Bigotti *et al.* (*supra*), Inaba *et al.* (*supra*), and Cohen *et al.*, (*supra*), as applied to claim 23, and further in view of Taylor *et al.* (of record) for the reasons of record in Applicants' prior response filed January 9, 2008. Briefly, the Examiner believes that the combination of Sallusto *et al.*, Bigotti *et al.*, and Inaba *et al.* suggests the compositions of the claimed invention. In addition, the Examiner believes that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to cryopreserve the dendritic cells taught by Sallusto *et al.*, Bigotti *et al.*, Stites (was Inaba *et al.* intended?), and Cohen *et al.*, using the cryopreservation method taught by Taylor *et al.*, to preserve the previously isolated dendritic cells for later use. Applicants must again disagree with the reasoning of the Examiner. In particular, as above, Sallusto *et al.*, Bigotti *et al.*, and Inaba *et al.*, do not teach the compositions of the present invention. Taylor *et al.* is directed to cryopreservation techniques and does not address the shortcomings in the teachings of Bigotti *et al.*, Sallusto *et al.*, Bigotti *et al.* and Inaba *et al.*, when considered individually or in any combination. As such, any combination of the references with Taylor *et al.* does not teach or suggest the composition as set forth in claims 28 and 29.

Claim 30 remains rejected under 35 U.S.C. § 103 as being obvious over Sallusto *et al.* (*supra*), Bigotti *et al.* (*supra*), and Inaba *et al.*, (*supra*), as applied to claim 23, and further in view of Taylor *et al.* (of record) as applied to claim 28, and Lutz *et al.* (of record), for the reasons of record. The Examiner has noted that the combination of Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.*, and Taylor *et al.* suggest the compositions of the claimed invention as set forth above. The Examiner believes that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the cryopreserved dendritic cells taught by Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.*, and Taylor *et al.*, using the immortalizing method

taught by Lutz *et al.*, because immortalizing dendritic cells would allow maintenance of dendritic cells *in vitro* for long periods of time.

Applicants must again disagree with the rejection of the Examiner, as above, the teachings of Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.*, and Taylor *et al.* when considered alone or in any combination do not disclose or suggest any composition of the present application. The teachings of Lutz *et al.* when considered either alone or in combination with any of the other cited references does not cure the deficiencies of the primary references, Sallusto *et al.* and Bigotti *et al.* in that Bigotti *et al.* does not disclose or even suggest to the skilled artisan that the S-100 labeled cells uptake and process prostate antigen. The Examiner's allegation regarding necrotic tumor cells is not relevant to Bigotti *et al.* because the low grade prostate tumors studied by Bigotti *et al.* do not have necrotic cells.

In summary, the Examiner alleges that the invention is obvious over the prior art. In particular, the Examiner has alleged that Bigotti *et al.* provides motivation for making dendritic cells *n vitro*, using the methods of Sallusto *et al.* because i) the presence of Langerhans cells and HLA class II molecules correlates with low grade prostate cancers, as compared with high grade cancers, and ii) this correlation with low grade prostate cancer is understandable, in view of a) both Langerhans cells and HLA class II molecules elicit the immune response, capable of direct antigen presentation to immune cells, b) Langerhans cells act as antigen presenting cells in neoplastic environments, and c) HLA class II molecules expressed by neoplastic glandular epithelium, with the aid of Langerhans cells, interact with macrophages and T helper lymphocytes, and cause expansion of cytotoxic T cells and enhancement of antibody response to membrane-bound tumor associated antigen. Further, the Examiner again alleges that the teachings of Bigotti *et al.* that macrophage play a primary role in controlling prostate tumor progression, but Langerhans cells, as antigen presenting cells, elicit the immune response, aiding

in the expansion of cytotoxic T cells and enhancement of antibody response to membrane-bound tumor associated antigen, actually provide motivation for making antigen presenting cells, such as dendritic cells, *in vitro*, as taught by the combined art, for potential treatment of prostate cancer patients, to complement the action of macrophage, and further enhancing the immune response to tumor antigen in prostate cancer patients.

Applicants again strongly disagree with the characterization of Bigotti *et al.* In particular, Bigotti *et al.* do not disclose that the Langerhans cells (the S-100 positive cells) up take any antigen much less a prostate antigen. Any suggestion regarding an involvement of the cells in an immune response is merely speculative and is not in keeping with the art accepted activity of antigen presenting cells. See paragraph 9 of the Bosch Declaration. Further, Bigotti *et al.* does not provide any evidence to support the induction of an anti-tumor immune response. First, Langerhans cells are known to be present in the interstitial space of most glandular tissues. Second, S-100 is not an exclusive marker for Langerhans cells, and is a marker for cells derived from the neural crest. The identification of the S-100-stained cells as Langerhans cells is questionable in Bigotti *et al.* because there is no mention of the presence of Birbeck granules. Third, Langerhans cells in any tissue stain strongly positive for HLA class II antigens, but this association is not found by Bigotti *et al.*, who state instead "we found that low-grade carcinomas were very rich in HLA-class II-positive, interstitial, oval to elongated cells, which sometimes were in close contact with tumor glands". These cells were further characterized by Bigotti *et al.* as representing macrophages and in only small percentages Langerhans cells. Fourth, there is no evidence of infiltrating T cells in the tumor, and therefore no objective evidence of the anti-tumor response postulated by the authors. As such, at most the findings of Bigotti *et al.* support a low level non-specific inflammatory environment mediated by infiltrating macrophages and as evidenced by class II expression on the tumor cells and the interstitial cells. No objective

evidence is presented that supports a functional role for Langerhans cells in these tissues, or for the induction of an immune response, let alone an immune response against cancer antigens. In fact, there is no mention of cancer antigens in Bigotti *et al.* Bosch Declaration, paragraph 6. Still further, The skilled artisan at the time of the present invention would have known that when contacted by a foreign antigen the antigen presenting cell would uptake the antigen becoming activated to mature; the activated Langerhans cell typically would migrate to a lymphatic tissue where the cell would complete maturation; upon maturation the antigen presenting cell would present antigen to T lymphocytes, including CD4+ and CD8+ T lymphocytes, wherein the T lymphocyte is activated; and the activated T lymphocyte, for example a tumor infiltrating lymphocyte, migrates back to the tumor. B lymphocytes can also be activated by this process to produce antibody specific for tumor associated antigens. It is important to note that the antigen must be "foreign" and that mechanisms are present *in vivo* to prevent a response to self-antigens. As such, there is no reasonable motivation or expectation for the skilled artisan to combine the *in vivo* observations of Bigotti *et al.* with the teaching of Sallusto *et al.* to further enhance the immune response to tumor antigens in prostate cancer patients.

In view of the above remarks, Applicants respectfully request the Examiner to reconsider and withdraw the various rejections of claims 23, 24, 26 and 28-37 under 35 U.S.C. § 103(a) as being obvious over Sallusto *et al.*, Bigotti *et al.*, as evidenced by Inaba *et al.*, in further view of Sites, Cohen *et al.*, Taylor *et al.* and or Lutz *et al.*

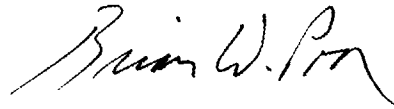
CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-695-1786.

Respectfully submitted,

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